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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,305	12/06/2001	Charles E. Prussak	041673-2092	1335

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EXAMINER

GAMBEL, PHILLIP

ART UNIT	PAPER NUMBER
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1644

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/006,305	Applicant(s) PRUSSAK ET AL.	
	Examiner Phillip Gambel	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 October 2006.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-4, 8, 11, 12, 14, 16-21, 23-29, 32-41, 43-51 and 62-75 is/are pending in the application.
 4a) Of the above claim(s) 14, 16-21, 23-26, 43-51 and 62-67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2-4, 8, 11-12, 27-29, 32-41 and 68-75 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Applicant's amendment, filed 10/5/06, has been entered.
Claims 2, 8, 68 and 69 have been amended.

Claims 2-4, 8, 11-12, 14, 16-21, 23-29, 32-41, 43-51 and 62-75 are pending.

Applicant's election without traverse of Group I for examination, and the species wherein Domains I, II and III are fragments of CD154 (i.e. CD40L), while Domain IV comprised a fragment of human TNF α has been acknowledged.

For examination purposes, the elected claims 2-4, 8, 11-12, 27-29, 32-41 and 68-75 are being examined to the extent they read on the elected species wherein Domains I, II and III are fragments of CD154 (i.e. CD40L), while Domain IV comprised a fragment of human TNF α .

Claims 14, 16-21, 23-26, 43-51 and 62-67 have been withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to the nonelected inventions and/or species.

Claims 1, 5-7, 9-10, 13, 15, 22, 30-31, 42, 52-61 have been canceled previously.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Action will be in response to applicant's arguments, filed 10/5/06.

The rejections of record can be found in the previous Office Action, mailed 8/1/06.

3. Claims 2-4, 8, 11-12, 27-29, 32-41 and 68-75 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kipps et al. (U.S. Patent No. 7,070,771) AND/OR Kipps et al. (WO 98/26061) in view of Mueller et al. (J. Biol. Chem. 274: 1999) (1449) essentially for the reasons of record.

Applicant's arguments, in conjunction with the Prussak 132 Declaration have been fully considered but have not been convincing essentially for the reasons of record.

In response to applicant's arguments that there is no or insufficient suggestion to combine the references to modify the prior art to render applicant's invention obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

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While applicant in conjunction with the Prussak Declaration appear to focus on the lack of sufficient motivation and expectation of success on the modifications suggested by Mueller et al. (J. Biol. Chem. 274: 1999).

it appears that such assertions appear to overstate the deficiencies of the prior teachings of Mueller et al., and more in particular, the teachings of the combined references.

In this case the teachings of the prior art references pertaining to the difficulties in preventing the deleterious effects of cleaved TNF α and, in turn, their teachings indicating success in generating chimeric accessory molecules to solve the same or similar problem would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve a well known problem in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144

As pointed out previously, both Kipps et al. (U.S. Patent No. 7,070,771 and WO 98/26061) (see entire documents) teach chimeric molecules, including nucleic acids encoding accessory molecules ligands (and associated vectors, including viral vectors and regulatory regions host cells such as tumor cells and antigen presenting cells and methods of producing the chimeric molecules) which are made up of various domains and sub-domains of molecules derived from the tumor necrosis factor molecules, which, in turn, contain unique properties which lead to the stabilization of their activities and greater usefulness in the treatment of diseases (see entire document, including Abstracts and Summary of the Inventions). The Detailed Description of the Invention these prior art references describe the very CD154 / CD40L domain structures to be utilized as well as TNF α itself as well as the Domain Structure of Tumor Necrosis Factor Family Molecules (e.g. see Table 1 on column 15 of U.S. Patent No. 7,070,771 and page 29 of WO 98/26061).

While the prior art Kipps et al. references contemplate chimeric accessory molecules comprising any domain, sub-domain and portions of the disclosed molecules, including CD154/CD40L and TNF α (e.g., see Detailed Description of the Inventions), these references do not set out the particular nucleic acid molecules comprising a Domain IV fragment of TNF α and the rest of the molecule comprising CD40L per se.

Also, as noted previously, these Kipps et al. references do note that the fourth domain (Domain IV) of the accessory molecule ligand gene(s) is called the distal extracellular domain and that the secondary structures of the accessory molecule(s) were deduced based upon CD40L and human TNF (e.g. see column 14-15, overlapping paragraph of U.S. Patent No. 7,070,771 and pages 27-28 of WO 98/26061).

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Further, the disclosures of the co-inventors own prior art references are very similar if not the same as the instant disclosure of generating chimeric accessory molecules comprising any domain, sub-domain and portions of the disclosed molecules, including CD154/CD40L and TNF α (e.g., see Detailed Description of the Inventions) as the instant disclosure.

While applicant and the Prussak Declaration acknowledge the teachings of Mueller et al., applicant submits that this reference only teaches modifying the wild-type TNF α in certain respects, including that the deletion of the cleavage site alone as not being sufficient to substantially eliminate soluble TNF release.

However, such a limited reading of Mueller et al. itself is not readily apparent and not found convincing with respect to the principles as well as advantages and expected beneficial results that would have been produced by their combination.

Again, the prior art is the same or nearly the same as the instant disclosure with respect to generating the same types of chimeric accessory molecules with the same direction to combining different elements of CD154/CD40L and TNF α to achieve the same or similar advantages and benefits as applicant's disclosure as filed.

As noted previously, Mueller et al. teach the advantages and, in turn, constructs comprising transmembrane TNF α , which include deleting proteolytic cleavage sites of TNF α to prevent the deleterious effects of cleaved TNF α (see entire document, including Abstract, Introduction and Discussion). Mueller et al. also discusses the role of TNF α in association with CD154 / CD40L as well as the use of transmembrane TNF α therapeutically (see Discussion, including page 38117, columns 1-2).

While Mueller's mutants were not human, the combined teachings including the Kipps' references clearly provided for the use of human constructs, particularly in light of their utilities in the treatment of humans.

Therefore, it would have been prima obvious to the ordinary artisan at the time the invention was made to construct nucleic acids encoding chimeric accessory molecules, including the construction of TNF α on the extracellular domain with domains of CD154 / CD40L in order to take advantage of the known uses of TNF α , but to avoid the deleterious effects of some or pleiotropic properties of TNF α , such as endotoxic shock, as taught by both Kipps et al. references and Mueller et al. Both Kipps et al. references clearly teach mixing and matching members of the TNF family and rely upon the predicted structures of TNF α and CD154/CD40L per se as a basis for their teachings of constructing chimeric accessory molecules. Nucleic acids comprising SEQ ID NO: 1 would have been an expected or intrinsic property of chimeric molecules comprising human TNF α linked to CD154/CD40L Domains I, II and III.

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One of ordinary skill in the art at the time the invention was made would have been motivated to select an extracellular domain of TNF α with CD154/CD40L domains to achieve the use of TNF α and to avoid the deleterious effects of TNF α by constructing chimeric accessory molecules which contain unique properties which lead to the stabilization of their activities and greater usefulness in the treatment of diseases, as taught by the Kipps et al. references.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One cannot show non-obviousness by merely asserting that the references do not provide the sufficient elements of obviousness or by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

Applicant's assertions of unexpected results is acknowledged, however the prior art provided sufficient motivation and expectation of success in constructing chimeric accessory molecules, including the construction of TNF α on the extracellular domain with domains of CD154 / CD40L in order to take advantage of the known uses of TNF α , but to avoid the deleterious effects of some or pleiotropic properties of TNF α , such as endotoxic shock, which in turn, is the same asserted advantages relied upon by applicant in the current application. Therefore, the asserted advantages and unexpected results appear to be the same or nearly the same as the instant application.

Applicant's arguments have not been found persuasive.

4. No claim is allowed.

5. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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60. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
December 26, 2006

